Seroprevalence of SARS-CoV-2 in an Asymptomatic US Population

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Research Article

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Abstract

Methods: We performed SARS-CoV-2 antibody tests with the Roche e602 SARS CoV-2 Immuno system on 50,257 consecutive life insurance applicants who were having blood drawn for the purpose of underwriting mortality risk. Other variables included height, weight, and blood pressure at the time of the blood draw, a history of smoking and common chronic diseases (hypertension, heart disease, diabetes, and cancer).

Results: The overall prevalence of SARS-CoV-2 was 3.0%, and was fairly consistent across the age range and similar in males and females. Geographical distribution revealed a very high level of positivity in the state of New York compared to all other areas (17.1%). Using US Census state population data to adjust state specific rates of positivity, it is estimated that this level of seropositivity would correspond to 6.98 million (99% CI: 6.56-7.38 million) SARS-CoV-2 infections in the US, which is 3.8 times the cumulative number of cases in the US reported to the CDC as of June 1, 2020.

Conclusions: The estimated number of total SARS-CoV-2 infections based on positive serology is substantially higher than the total number of cases reported to the CDC. There is no apparent increase of risk of infection for individuals self-reporting, smoking, diabetes, heart disease, hypertension or cancer.

Introduction

In early 2020 a novel coronavirus emerged in Hubei Province, China1. The causative agent was a betacoronavirus most closely related genetically to zoonotic viruses found in bats, and clinically similar to recent emergent epidemic coronaviruses which caused Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS)2. Since then, the virus has become a worldwide pandemic, infecting over 17 million persons and causing more than 660,000 deaths as of this writing3. The first case in the United States occurred on January 20th, 20204. And since then the Centers for Disease Control and Prevention has recommended that all states report laboratory-confirmed cases5. Case counts have been closely tracked by the CDC, the press, and academic institutions. However, because the illness caused by SARS-CoV-2 may be asymptomatic or minimally symptomatic6, these counts of cases may underestimate the number of persons who have been infected. Various studies of seroprevalence in the United States7,8 have shown different results based on timing and locality, but have been consistent in showing that seroprevalence is higher than would be implied by simple case counts based on viral antibody testing.

Because SARS-CoV-2 is novel, the presence of antibodies in the blood likely indicates a history of infection since the pandemic began, and serologic testing can be used to estimate the overall rate of infection, even in those who had minimal symptoms or who were never tested despite symptoms.

In this study, a convenience sample of blood specimens submitted to a commercial laboratory was used to conduct a survey of seroprevalence. The goal was both to estimate the overall number of cases in the

general population and to examine the data to determine if smoking or any common chronic illnesses were significantly associated with seropositivity.

Methods

In the United States, the process of purchasing life insurance often involves a brief physical examination by paramedical professionals, the collection of height, weight and blood pressure measurements, and the testing of blood and urine specimens for common laboratory test related to overall health. Such tests are seldom, if ever, performed on individuals below age 17 years or above 85 years. Also, blood tests are generally reserved for individuals applying for higher dollar amounts of life insurance or for those applying for permanent types of insurance (rather than term insurance). Thus, individuals applying for life insurance are a self-selected group primarily from higher socio-economic strata. Those who have a history advanced chronic illness may be less likely to apply because more serious conditions can be associated with higher premiums.

Between May12th and June 25th 2020, 50,257 individuals were tested for antibodies to SARS-CoV-2. Individuals were part of a convenience sample from a pool of life insurance applicants who had blood tests performed as part of life insurance underwriting. This sample represents approximately one fifth of all samples tested at the facility during that time. All applicants self-reported that they were well at the time of application. The antibody tests were performed using the Roche Elecsys Anti-SARS-CoV-2 kit on the Roche e602 analyzer, with a stated sensitivity of 100% and specificity of 99.8%, utilizing an electrochemiluminescence immunoassay.

Western IRB reviewed the study under the Common Rule and applicable guidance and determined it is exempt under 45 CFR § 46.104(d)(4) using de-identified study samples for epidemiologic investigation.

Other information available on test subjects included age, sex, smoking status (tobacco use within one year), height, weight, and blood pressure, and routine laboratory measures which included, glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyltransferase, alkaline phosphatase, total bilirubin, total cholesterol , high density lipoprotein (HDL) cholesterol, triglycerides, and some tested for lactate dehydrogenase, hemoglobin A1c, and NT-pro B-type natriuretic peptide.

Limited medical history was available in the form of responses to simple yes/no questions regarding a history of cardiovascular disease, diabetes, hypertension, and cancer.

The differences in continuous variables between the antibody-positive and negative groups were tested for significance with the Mann-Whitney U test, while differences in categorical variables were tested using the chi-square test.

To estimate the total burden of SARS-CoV-2 infections in the US, census data was obtained. For each state and the District of Columbia, the total 2018 estimated census population was multiplied by the US population proportion between the ages of 20 and 80 (71.1%). Then, the state-specific proportion of positive tests was applied from our sample. Confidence limits were estimated by generating 5000 bootstrap samples (with replacement) of our data and recalculating the total number of US cases. Under and over-representation of states was determined by a ratio between the proportion of individuals living in a given state to the proportion of tests performed in that state.

All statistical analyses were performed using R (version 3.6.1)[9] and R-studio (version1.2.1335)[10].

Results

The overall sample included 50,025 individuals with a median age of 42 years (IQR: 34-54), 56% of whom were male. Geographical distribution deviated somewhat from the overall population distribution of the US, with some under-representation from Maine, West Virginia, Vermont and Oklahoma, and over-representation from Nebraska, Hawaii, and Utah. Characteristics of the study population are displayed in Table 1. The antibody positive group tended to be slightly younger (median age 41) vs. the antibody negative group (median age 42). The proportion of subjects reporting a history of smoking, heart disease, hypertension and/or diabetes was similar between the positive and negative groups.

This study estimated the seroprevalence of SARS-CoV-2 antibodies in a geographically diverse sample of adults in the US within a 6-week collection period ending in late June 2020. The rate of positivity ranged from 0% to 17% by state and from 1-3% across age and sex categories. The choropleth map of seropositivity roughly corresponds to the areas where the most COVID-19 cases were reported during that period of time. Our results suggest that many more infections occurred than were reported. This is likely due to asymptomatic or minimally symptomatic infections for which care was not sought or symptomatic infection for which testing was not available or obtained.

Various studies have been published, both before and after peer review, which have reported seroprevalence of SARS-CoV-2 antibodies in the US. Most notably, Havers et al[11]. evaluated a convenience sample (n=16,025) of serological tests on sera submitted to 2 commercial laboratories from 10 US regions. Their estimates of seroprevalence ranged from 1% to 7%, with the highest rates occurring in the New York City metro area, Louisiana and Connecticut. The timeframe of this testing differed by region and was earlier than the current study. The authors estimated that the seroprevalence implied that between 6 and 24 times the number of infections had occurred in the studied regions than had been reported.

Stadlbauer et al reported on longitudinal changes in seroprevalence in New York City between late February and mid-April 2020 [12]. Over this period of time seroprevalence increased from 2.2% to 10.1%. Rosenberg et al also reported on seroprevalence in the New York metro area[13]. The collection period was from April 19 to 28, 2020, and the estimate was 22.7%. The higher estimate than the current study, despite being performed in an earlier time period, is likely due to a geographical distribution that is more localized to the highest prevalence metro region, rather than the entire state of New York.

We report that, around the time of study, the number of infections in the US was nearly 4 times higher than cases of infection reported suggesting a much more widespread pandemic, but with a smaller rate of hospitalization, complications and deaths. Weaknesses of the study include the imbalanced representation of the US states, as well as the lack of samples from those under age 20 or over age 80. The age distribution is also more heavily weighted to the young adult years, which is not representative of the US population. Although the sample size was large, it was not large enough to stratify by both age and geography when estimating population seroprevalence. Finally, the life insurance-buying population tends to be both healthier and wealthier than average, and this could also bias the results in an indeterminate direction.

Conclusion

The rate of SARS-CoV-2 seropositivity in this population of insurance applicants implies a burden of infection approximately 3.8 times higher than the number of reported cases. There was no apparent increase in risk of being COVID-19 positive for self-reported smoking and or chronic health problems.

Declarations

Both authors contributed equally to the development of this data, the statistical analysis, writing and review of this article. We wish to extend a special thanks to Dr Michael Fulks for reviewing and providing

valuable suggests for this article.

The data for this study is registered at www.DATADRYAD.ORG SEROPREVALENCE OF SARS-CoV-2 ANTIBODY in an ASYMPTOMATIC POPULATION submitted with DOI https://doi.org/10.5061/dryad.b5mkkwhbg.

The data are in an Excel file format.

Abbreviations include Rea=reactive, non_rea= non reactive, N/S=not specified, blank= no response, no age or sex=date of birth or sex not reported.

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Western Institutional Review Board's (WIRB's) IRB Affairs Department reviewed the study under the Common Rule and determined it is exempt under 45 CFR § 46.104(d)(4) using de-identified study samples.

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Tables

Table 1: Characteristics of study population by SARS-CoV-2 antibody status.

Numeric values shown as median [IQR].

1 p-value by Chi-square test. 2 p-value by Mann-Whitney U test.

	SARS-CoV-2 negative n = 48,505	SARS-CoV-2 positive n = 1,520	p
Age (yrs)	42 [34,54]	41 [33,52]	<0.001[2]
18-40	47.8%	50.7%	
41-60	40.2%	41.4%	0.55[1]
61-85	12.0%	7.8%	
Sex, (% male)	55.8%	53.9%	0.15[1]
Current Smoker	4.1%	3.1%	0.05[1]
Heart Disease	1.2%	1.0%	0.61[1]
Hypertension	15.2%	15.4%	0.84[1]
Diabetes	4.9%	4.6%	0.66[1]

Table 2: Rate of SARS-CoV-2 Antibodies by Age and Sex

Age Range	Female	Male
20-30	3.6%	3.4%
31-40	3.1%	3.1%
41-50	3.7%	3.0%
51-60	3.1%	2.7%
61-70	2.0%	2.5%
71-80	1.0%	1.1%

Table 3: Prevalence of SARS-CoV-2 Antibodies by Location

AK	0.0%	**KY**	1.0%	**NY**	17.1%
AL	1.5%	**LA**	3.8%	**OH**	0.9%
AR	1.4%	**MA**	4.2%	**OK**	0.5%
AZ	1.1%	**MD**	4.3%	**OR**	1.0%
CA	1.5%	**ME**	0.0%	**PA**	2.6%
CO	1.2%	**MI**	4.4%	**RI**	4.3%
CT	6.0%	**MN**	2.2%	**SC**	1.0%
DC	5.1%	**MO**	1.9%	**SD**	2.2%
DE	3.3%	**MS**	2.2%	**TN**	0.5%
FL	2.0%	**MT**	0.8%	**TX**	1.1%
GA	2.7%	**NC**	1.1%	**UT**	0.7%
HI	0.7%	**ND**	0.8%	**VA**	1.2%
IA	1.5%	**NE**	2.1%	**VT**	1.7%
ID	0.7%	**NH**	1.8%	**WA**	1.1%
IL	3.7%	**NJ**	9.2%	**WI**	1.3%
IN	2.0%	**NM**	0.5%	**WV**	0.9%
KS	1.6%	**NV**	2.4%	**WY**	0.0%

Figures

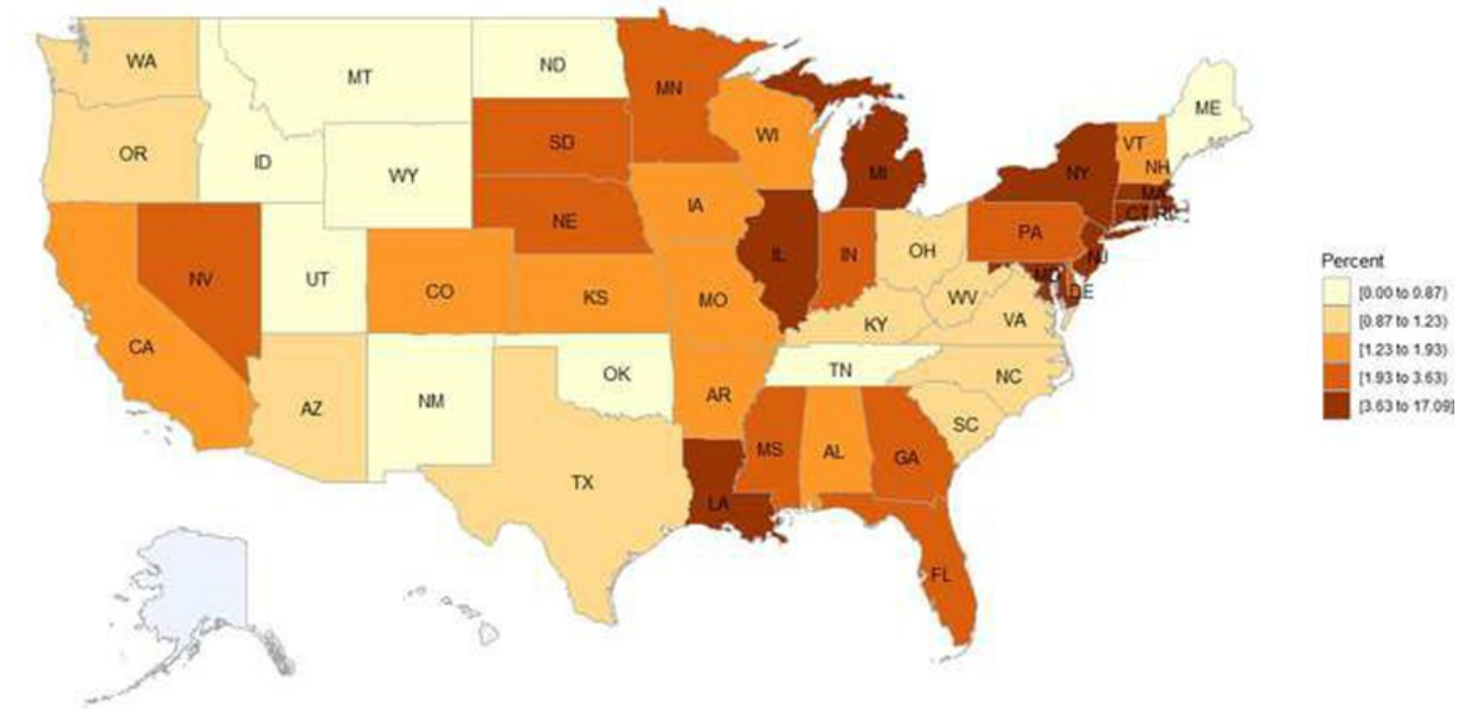

Figure 1

SARS-CoV-2 Seroprevalence